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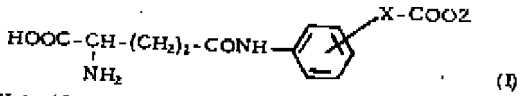
44111 E/22 805 MITU 12.11.80
MITSUBISHI CHEM IND KK (NNSH)
12.11.80-JP-159320 (+159319) (26.05.82) A61k-37/02 C07c-103/52 *EP--52-296

Glutamine derivs. - useful as immuno:modulating agents with immunosuppressive and immunostimulating activities

D/S: E(AT BE CH DE FR GB IT LI NL SE)
Full Patentees: Mitsubishi Chem. Ind. Ltd. and Nippon Shinyaku Co. Ltd.

Glutamine derivs. of formula (I) and their salts are new.



(I)

(X is $(CH_2)_n$, vinylene or CR_1R_2;
n is 1-4;
R_1 and R_2 are each H or 1-4C alkyl, at least one being other than H; and
Z is H or 1-4C alkyl).

USES

Cpds. (I) have immunomodulating activity, including immunosuppressive and immunostimulating activities, and so are useful for treating autoimmune diseases, allergic conditions, cancer, bacterial infections, etc. Dose is 0.1-100 mg/kg parenterally daily or 0.001-1 g/kg orally daily.

PREPARATION

Methods used include:
(1) reaction of an amino-protected glutamic acid anhydride with a YO-CO-X-substd. aniline (II) (Y is 1-4C alkyl), then the protecting gp. is eliminated. The protecting gp. for the NH_2 may include incorporation in a phthalimido gp.;
(2) reaction of glutamic acid, having the α-COOH and α-NH_2 protected, with (II) in the presence of an activating agent; then protecting gps. are removed; and
(3) reaction of a reactive deriv. at the γ-carboxyl of glutamic acid, having the α-COOH and α-NH_2 protected, with (II); then protecting gps. are removed.

EXAMPLE

74.28 g N-benzyloxycarbonyl-L-glutamic acid α-benzyl ester and 28 ml NEt_3 were added to a mixt. of 250 ml THF and 250 ml DMF. The mixt. was stirred with ice-cooling and 26.4 ml ClCOOiBu was added dropwise. The mixt. was stirred for 15 mins., then 35.84 g Et p-aminophenylacetate in 50 ml DMF was added and the mixt. stirred for 30 mins., with ice cooling, then for 8 hrs. at room temp. The solvent was evapd. and the residue purified to give an intermediate, which was catalytically hydrogenated (Pd black) in aq. EtOH to give N-(4-ethoxycarbonylmethylphenyl)glutamate, m.pt. 179.8-180.5°C.(69pp1248).
(E)ISR:- J55026870 GB2034690 US4167449 J55036428 J55036454 3.Jnl.Ref

B(10-B2E, 12-A1, 12-A6, 12-D2, 12-G7) 4
32

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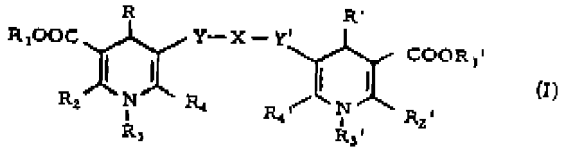
44113 E/22 803 FARB 13.11.80
BAYER AG
13.11.80-DE-042769 (26.05.82) A61k-31/44 C07d-211/90 C07d-401/14 C07d-405/14 C07d-409/14 C07d-413/14 *EP--52-300

C3-Linked 4-aryl-1,4-dihydro-pyridine-3 carboxylic acid derivs. - with cardiovascular e.g. antihypertensive, vasodilator, cerebral or coronary activity

D/S: E(AT BE CH DE FR GB IT LI LU NL SE)

C3-linked 4-aryl-1,4-dihydro-pyridine-3-carboxylic acid derivs. of formula (I) and their salts are new.



(I)

(R and R' are aryl, thienyl, furyl, pyrryl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, naphthyl, quinolyl, isoquinolyl, indolyl, benzimidazolyl, quinazolyl or quinoxalyl all opt. mono-, di- or trisubstd. by phenyl, alkyl, alkenyl, alkoxy, alkenyloxy, alkylene, dioxyalkylene, halogen, mono- or polyfluoroalkyl, mono- or polyfluoro-alkoxy, OH, NH_2, alkylamino, NO_2, CN, N_3, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl and SO_2-alkyl;
R_1 and R_1' are opt. branched or cyclic, opt. unsatd. hydrocarbon residues opt. interrupted by 1 or 2 O and opt. substd. by halogen or OH or by phenyl, phenoxy, phenylthio or phenylsulphonyl (all opt. substd. by halogen, CN, dialkylamino, alkoxy, alkyl, CF_3 or NO_2);
R_2, R_2', R_4 and R_4' are H or an opt. cyclic, opt. unsatd. hydrocarbon residue opt. substd. by halogen, OH, aryl or amino (opt. substd. by opt. substd., opt. cyclic, opt. unsatd. hydrocarbyl);
R_3 and R_3' are H, opt. substd. aryl or aralkyl, or opt. substd. alkyl the chain of which may be interrupted by 1 or 2 O;
Y and Y' are -CO-O-, CONH, CO-S, CO or SO_2;
X is a bridging gp. with ≥ 1 CH_2 and ≤ 9 adjacent CH_2, the bridging gp. also contg. (in any order) 1-5 chain members selected from O, S, SO, SO_2, CO, CS, NR_5, $C(R_6)_2$, $C(R_6)=C(R_6)$; C≡C, CH=CH, CH=N, arylene, heteroarylene, cycloalkylene, cycloalkenylene, piperazinylene, piperidylene, pyrrolidinylene and morpholinylene;
R_5 is H, alkyl or aralkyl; and

B(6-H, 7-D4, 12-C10, 12-E1, 12-F1, 12-F5, 12-F7) 5
33

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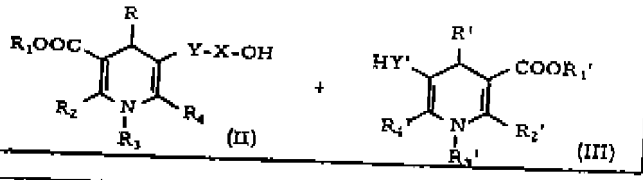
R_4 is H, aralkyl, aryl, heteroaryl, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, alkylene, dioxyalkylene, halogen, mono- or polyfluoroalkoxy, mono- or polyfluoroalkyl, OH, NH_2, alkylamino, NO_2, CN, N_3, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or SO_2-alkyl, the aryl, heteroaryl and alkyl residues opt. mono-, di- or tri-substd. by aryl, alkyl, alkoxy, aralkyl, dioxyalkylene, halogen, mono- or polyfluoroalkyl, mono- or polyfluoroalkoxy, OH, NH_2, alkylamino, NO_2, CN, N_3, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or SO_2-alkyl).

USE

(I) have cardiovascular activity and can be used as antihypertensives, vasodilators, cerebral agents and coronary agents. They have a partic. prolonged duration of action.

PREPARATION

E.g.



(II) + (III)

-H_2O → (I)

The reaction is in an inert organic solvent at 0-180°C in the presence of dehydrating agents using equiv. amts. of (II) and (III).

EXAMPLE

2,6-Dimethyl-5-(4-hydroxybutoxy-carbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid ethyl ester (25 mmol), DCC (25 mmol) and 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid (25 mmol) in anhydrous DMF (50 ml) are heated 4 hrs. at 100°C with 4-dimethylaminopyridine (0.2 g), then worked up to give 2,6-dimethyl-5-etnoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid 1,4-butanediyl este. as an amorphous foam in 25% yield.(53pp280).

(G) ISR: DE2847236 DE1795791 DE2117571

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44121 E/22 B03

STERLING DRUG INC

24.08.81-US-297759 (+208259) (26.05.82) C07d-211/26

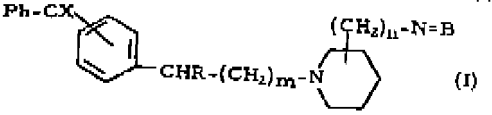
STER 19.11.80

*EP --52-311

N-Benzoyl-phenyl-alkyl-piperidine derivs. and analogues - useful as bronchodilators, anti-asthmatics, anticholinergics

D/S: E(BE CH DE FR GB IT LI LU NL SE).

N(Benzoylphenylalkyl)piperidine derivs. and analogues of formula (I) and their acid-addn. salts are new.



(I)

[R is H or 1-6C alkyl;
m is 0 or 1;
n is 0 or 1;
N=B is 1-piperidinyl, 4-morpholinyl, NH_2, di-(1-6C)alkylamino, 1-6C alkanoylamino, N-(1-6C)alkyl-N-(1-6C)alkanoylamino, cycloalkanecarbonylamino, or PhCONH opt. ring substd. by 1-6C alkyl, halogen or 1-6C alkoxy;
CX is CO or CH(OH);

B(7-D5, 12-D2, 12-E4, 12-G1, 12-K2)

3 4

PhCX is attached to the 3- or 4-posn. when m is 1 or only to the 3-posn. when m is 0;
provided that when m is 0, n is 1, R is alkyl and N=B is 1-piperidinyl or 4-morpholinyl).

USES

(I) are bronchodilators, antiasthmatics, antiallergics, anticholinergics and prostaglandin synthetase inhibitors.

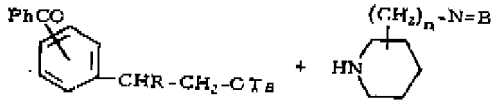
SPECIFICALLY CLAIMED

8 Cpds. (I), including 1-(2-(3-benzoylphenyl)propyl)-4-acetylaminopiperidine HCl and the corresp. 4-benzoyl cpd.

PREPARATION

Methods used include:

(1)



acid acceptor → (I, m is 1, CX is CO)

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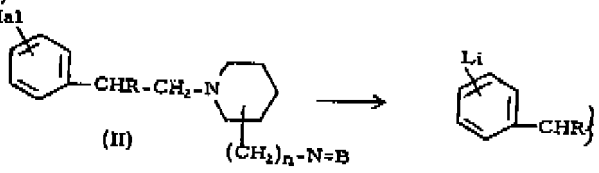
Ts is toluene-p-sulphonyl).

(2)



(II)

(1) Benzonitrile
(2) Hydrolysis → (I; m is 1, CX is CO)

(3) When m is 1, redn. of a corresp. ketone, i.e. with a CHR-CO- bridge, with $LiAlH_4$ gives the prod. When CX is CO, it may be protected by ketalisation etc.

EXAMPLE

10.17g α-(3-benzoylphenyl)propionic acid in 25 ml benzene was treated with 9.52g $SOCl_2$ and refluxed for 3.25 hrs. The mixt. was evapd. and the residual oil in 25 ml CH_2Cl_2 was added to 4.86g NEt_3 and 7.29g 4-(1-piperidinylmethyl)-piperidine over 15-20 mins. at about 5°C. The mixt. was stirred for 3 hrs., washed with water, aq. $NaHCO_3$ and aq. NaCl, filtered and evapd. to give 1-(α-(3-benzoylphenyl)-propionyl)-4-(1-piperidinylmethyl)piperidine as an oil. It formed a HCl salt, m.pt. 211-212°C.(42pp1248).

(E) ISR: GB1250719 US3816434 GB1508391 FR1549342 US4216326.

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